Published in final edited form as:

Mov Disord. 2010 January 30; 25(2): 179–188. doi:10.1002/mds.22946.

Progressive supranuclear palsy syndrome presenting as progressive nonfluent aphasia: a neuropsychological and neuroimaging analysis

Jonathan D. Rohrer, MRCP^{#1}, Dominic Paviour, PhD MRCP^{#1,2}, Adolfo M. Bronstein, MD FRCP³, Sean S. O'Sullivan, MRCP², Andrew Lees, MD FRCP², and Jason D. Warren, PhD FRACP¹

¹Dementia Research Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

²Reta Lila Weston Institute, UCL Institute of Neurology, University College London, Queen Square, London, WC1N 1PJ, UK

³Department of Clinical Neuroscience, Charing Cross Hospital, Imperial College, London, UK

These authors contributed equally to this work.

Abstract

There is currently considerable interest in the clinical spectrum of progressive nonfluent aphasia (PNFA) and progressive supranuclear palsy (PSP) and the intersection of these two entities. Here we undertook a detailed prospective clinical, neuropsychological and neuroimaging analysis of 14 consecutive patients presenting with PNFA to identify cases meeting clinical criteria for PSP. These patients had further detailed assessment of extrapyramidal and oculomotor functions. All patients had high-resolution MR brain volumetry and a cortical thickness analysis was undertaken on the brain images. Four patients presenting with PNFA subsequently developed features of a PSP syndrome including a typical oculomotor palsy. The neuropsychological profile in these cases was similar to other patients with PNFA, however with more marked reduction in propositional speech, fewer speech errors, less marked impairment of literacy skills but more severe associated deficits of episodic memory and praxis. These PSP-PNFA cases had less prominent midbrain atrophy but more marked prefrontal atrophy than a comparison group of five patients with pathologically-confirmed PSP without PNFA; and more prominent midbrain atrophy but less marked perisylvian atrophy than other PNFA cases. In summary, although the PSP-PNFA syndrome overlaps with PNFA without PSP certain neuropsychological and neuroanatomical differences may help predict the development of a PSP syndrome.

Pre-publication corresponding author: Dr Jonathan D Rohrer, Dementia Research Centre, Institute of Neurology, Queen Square, London WC1N 3BG, UK; rohrer@dementia.ion.ucl.ac.uk. **Post-publication corresponding author:** Address correspondence and reprint requests to Dr Jason D Warren, Dementia Research Centre, Institute of Neurology, Queen Square, London WC1N 3BG, UK; warren@dementia.ion.ucl.ac.uk; tel: 44 207 829 8773; fax: 44 207 676 2066.

AUTHOR ROLES

All authors were involved in the conception and design of the study and in the review and critique of the manuscript. JDR executed the study and statistical analysis and wrote the first draft of the manuscript.

FINANCIAL DISCLOSURES

The authors have no other financial disclosures or any conflicts of interest

Keywords

primary progressive aphasia; progressive supranuclear palsy; apraxia of speech

INTRODUCTION

Progressive nonfluent aphasia (PNFA) is a degenerative disorder which presents with speech production impairment (1,2). However, although speech impairment dominates the early clinical presentation in PNFA, a parkinsonian disorder often co-occurs as the disease progresses. The overlap of PNFA and corticobasal syndrome (CBS) has been well-described (3,4) but more recently, cases have been reported with a progressive supranuclear palsy (PSP) syndrome (5,6,7,8,9,10). The language impairment in these cases is usually a disorder of speech production which has been described variously as the PNFA subtype of frontotemporal lobar degeneration (FTLD), progressive apraxia of speech (AOS), primary progressive aphasia (PPA), anomia or aphemia. This variation is probably at least in part attributable to the inconsistent terminology that has been used to describe speech production disorders (11). Patients presenting with a progressive “nonfluent” language disorder may have several distinct kinds of impairment including articulatory deficits (or AOS), agrammatism, reduced speech rate, severe word-finding difficulty or anomia. According to an emerging consensus, agrammatism and/or AOS are core features of the PNFA syndrome (1,12). It has been proposed that PNFA so defined, and in particular the presence of AOS, predicts tau-positive histopathologies, including PSP (4,7). In this study we aimed to investigate prospectively the clinical, neuropsychological and neuroimaging features of patients presenting with PNFA who subsequently developed characteristic features of PSP. We compared the clinical and neuroanatomical characteristics of these cases with established cases of PNFA without PSP syndrome and with pathologically confirmed classical PSP (Richardson’s syndrome, PSP-RS) cases without speech or language impairment.

METHODS

Clinical assessment

14 consecutive patients presenting with a clinical syndrome of PNFA to the tertiary Specialist Cognitive Disorders Clinic of the National Hospital for Neurology and Neurosurgery, London, UK, during a three-year period were assessed by an experienced cognitive neurologist (JW, JR). As part of this assessment all patients had a structured clinical history, neurological examination, Mini-Mental State Examination (MMSE, 12) and Frontal Assessment Battery (FAB, 13). A diagnosis of PNFA was made according to modified Neary criteria (1,2). Clinical features of a PSP syndrome at presentation or developing subsequently were also recorded (14,15): we refer to these cases hereafter as ‘PSP-PNFA’, and use ‘PNFA’ to refer to those cases not developing a PSP syndrome. All patients with clinical features of PSP-PNFA were further assessed using the activities of daily living (part II) and motor (part III) components of the Unified Parkinson’s Disease Rating Scale (UPDRS). In addition, a video analysis of oculomotor function in these cases

was undertaken by a neurologist with experience in degenerative movement disorders (DP) and the severity of any gaze abnormality assessed (16,17).

Neuropsychological assessment

A neuropsychological battery with a neurolinguistic focus was administered to all patients and to 14 cognitively-normal control subjects (matched for age and gender; Table 1). Background neuropsychological tests comprised a general (nonverbal) intelligence test (Raven's Advanced Progressive Matrices, 18) and tests assessing focal cognitive domains including episodic memory (Camden Pictorial Recognition Memory Test, 19), visuoperceptual skills (the Object Decision subtest of the Visual Object and Space Perception Battery, VOSP, 20) and executive function (Trail Making Test, 21). Limb apraxia was assessed as part of the clinical examination.

The neurolinguistic component of the battery assessed a number of key speech and language functions. Spontaneous speech was analysed from a sample obtained by asking subjects to talk about their last holiday and to describe the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination (22). This sample was recorded and subsequently transcribed and analysed for the number of words produced per minute, number of speech production (i.e. phonemic or phonetic) errors and agrammatic (incorrect tense/plural) errors made per minute and presence and severity of AOS (mild, moderate or severe). Naming was assessed using the Graded Naming Test (23) whilst comprehension was evaluated using the Warrington synonyms test for single words (24) and a shortened version of the PALPA55 test for sentences (25). Repetition of mono- and polysyllabic words and sentences was also tested (26). Reading was assessed using a 30-item irregular word reading test as well as the Graded Nonword Reading Test (27), and spelling was evaluated with the Graded Difficulty Spelling Test (28). Comparisons between the groups were performed using a linear regression model taking age and gender into account (STATA8, Stata Corp, College Station, Tex).

Brain imaging analysis

All patients and control subjects had volumetric T1-weighted MR brain images acquired on a 1.5T GE Signa scanner (General Electric, Milwaukee, WI). Five patients with pathologically-confirmed PSP-RS without a PNFA syndrome during life who had been imaged on the same scanner with the same MRI volumetric protocol constituted an additional comparison group. This group comprised four males and one female with a mean age at scan of 68.9 years (standard deviation 4.0). Estimated mean duration from symptom onset was 4.4 (standard deviation 1.3) years. Image analysis was performed using the MIDAS software package (29). Scans were outlined using a rapid semi-automated technique which involves interactive selection of thresholds, followed by a series of erosions and dilations. This yielded a brain region which was separated from surrounding cerebrospinal fluid (CSF), skull and dura. A baseline brain volume was calculated using this region in all subjects. Scans were subsequently transformed into standard space by registration to the Montreal Neurological Institute (MNI) Template (30). Manual segmentation of the midbrain was conducted to determine the midbrain volume using a previously described protocol (31). In brief, two orthogonal views were used to define a superior cut-off (upper border of the

midbrain tegmentum in the mid-sagittal slice), an inferior border at the superior border of the pons in the mid sagittal slice, and anterior and posterior borders defined by the brain tissue/CSF boundary (interpeduncular cistern anteriorly, and including the quadrigeminal plate). Brain and midbrain volumes were expressed as a percentage of the total intracranial volume.

Cortical reconstruction and thickness estimation was performed with the Freesurfer image analysis suite (32, 33) as previously described (34). A vertex-by-vertex analysis using a general linear model was performed to examine differences in cortical thickness between the disease groups and the control group. Cortical thickness, C , was modelled as a function of group, controlling for age and gender by including them as nuisance covariates. $C = \beta_1 \text{PSP-A} + \beta_2 \text{PNFA without PSP} + \beta_3 \text{PSP-RS} + \beta_4 \text{controls} + \beta_5 \text{age} + \beta_6 \text{gender} + \mu + \varepsilon$ (where μ is a constant, and ε is error). Contrasts of interest between the estimates of the group parameters were assessed using two-tailed t-tests. Maps showing statistically significant differences between the groups were generated and for the comparison with controls, corrected for multiple comparisons by thresholding the images of t-statistics to control the False Discovery Rate (FDR) at a 0.05 significance level.

Literature review

In order to assess the present series in relation to previously reported cases of PSP with PNFA, we conducted a search of the published literature using the MEDLINE internet database (www.ncbi.nlm.nih.gov/sites/entrez/) and the keywords “PSP”, “progressive supranuclear palsy”, “gaze palsy”, “PNFA”, “FTLD”, “PPA”, “apraxia of speech”, “progressive aphasia” and “aphasia”, in isolation and in combination. For all papers identified, the clinical details of all cases with pathological confirmation were abstracted. Age at onset, disease duration and age at death were recorded as well as clinical features at presentation and later in the disease course. Whether the cases would meet current research criteria for a diagnosis of PSP (15) was also recorded.

RESULTS

Clinical features

Four of 14 patients presenting with PNFA exhibited clinical features of PSP. Each of these patients had initially developed speech production impairment and only later in the disease course developed features of PSP. Over the same time period two other patients with PNFA developed features of a corticobasal syndrome (35). The group of PSP-PNFA cases and the group of other PNFA cases were comparable in terms of age, gender, and clinical disease duration (Table 1). In these cases the mean time from onset of language symptoms to development of features of PSP was 4.9 years (range 3.0 to 8.5 years) for gaze palsy and 4.0 years (range 1.0 to 8.0 years) for falls. The patients with PSP-PNFA had mean (standard deviation) scores of 20.0 (6.3) for UPDRS part II and 30.5 (15.8) for UPDRS part III compared to the scores for the five patients with pathologically proven PSP of 18.0 (7.2) for part II and 17.2 (7.2) for part III. The four PSP-PNFA subjects had clear supranuclear abnormalities of their eye movements with slow and hypometric vertical and horizontal saccades of similar severity to the cases with pathologically proven PSP.

Neuropsychological assessment

The pattern of neuropsychological and neurolinguistic deficits exhibited by patients with PSP-PNFA was similar to other PNFA patients (Table 1). On the general neuropsychological assessment (Table 1), relative to healthy controls both groups had impaired executive function and reduced digit span but intact visuoperceptual skills. The PSP-PNFA group had mildly impaired performance on a recognition memory task, and a higher incidence of limb apraxia than the other PNFA cases. On the detailed neurolinguistic assessment (Table 1), spontaneous speech analysis was broadly similar in both disease groups. PSP-PNFA and PNFA cases showed similar mean severity of apraxia of speech and number of agrammatic errors. However, the mean overall speech rate (words / minute) was substantially (though non-significantly) lower in the PSP-PNFA group than in the other PNFA cases, while speech production errors were significantly more frequent than healthy controls only in the PNFA group. Relative to healthy controls, performance on comprehension, repetition and reading tasks was impaired in the PNFA group but not the PSP-PNFA group, however the performance of the two disease groups did not differ significantly. Spelling was significantly more impaired in the PNFA group than the PSP-PNFA group.

Brain imaging analysis (Table 2 and Figures 1 and 2)

Mean total brain volume as a percentage of intracranial volume was significantly smaller than controls only in the PNFA group. Mean midbrain volume was smaller than controls in the PSP-PNFA and PSP-RS groups. Mean midbrain volume in the PSP-PNFA group was significantly smaller than the PNFA group but significantly larger than the PSP-RS group (Table 2).

Cortical thickness maps showed a characteristic pattern of predominantly left hemispheric atrophy in the PNFA group compared to the control group with most significant thinning of inferior frontal and superior temporal cortices (Figure 1A). The PSP-PNFA group had significant cortical thinning mainly in the left inferior and superior frontal lobe (Figure 1B). There were no significant areas of cortical thinning in the PSP-RS group compared to controls. There were no significant differences in cortical thickness between any of the disease groups when compared directly and corrected for multiple comparisons. Uncorrected significance maps and percentage thickness difference maps between groups are shown in Figure 2: cortical thickness was reduced in bilateral prefrontal areas in PSP-PNFA compared to PNFA (blue areas in Figure 2A); in a more extensive network of predominantly left-sided and mainly prefrontal areas in PSP-PNFA versus PSP-RS (blue areas in Figure 2B); and in superior and mid-temporal and posterior peri-Sylvian areas in PNFA versus PSP-PNFA (red/yellow areas in Figure 2A); there were no significant areas (at an uncorrected level of $p=0.05$) of cortical thinning in PSP-RS versus PSP-PNFA (Figure 2B).

Summary of published literature

A total of 12 cases of PSP presenting with a speech production disorder from seven separate studies were identified (Table 3: 5,6,7,8,9,10,36). The diagnosis during life in these cases was most commonly recorded as PNFA, nonfluent dysphasia, PPA or AOS. Ten of the 12 cases were examined at post mortem and five classified as having typical PSP pathology.

Atypical PSP pathology, or combinations of pathological abnormalities with PSP as the predominant diagnosis were identified in the five remaining cases (Table 3). The clinical features of the four cases presented in this study are included in Table 3 for comparison with the previously presented cases. The age at onset, disease duration and age at death of these cases did not differ significantly from other phenotypes of pathologically-proven PSP (classical PSP or Richardson's syndrome, PSP-RS, PSP-Parkinsonism or PSP-P and pure akinesia with gait freezing or PAGF: data from 37,38) (Table 4). However disease duration was closer to the classical PSP phenotype (RS) than to PSP-P or PAGF.

DISCUSSION

Here we have characterised the syndrome of progressive nonfluent aphasia/apraxia of speech with clinical features of PSP. The neuropsychological and neurolinguistic profile of PSP-PNFA is similar to PNFA (Table 1), consistent with the extensively overlapping pattern of cortical atrophy in these two syndromes (Figure 1). However, the syndromes do differ in certain respects: compared with PNFA, PSP-PNFA is associated with more profound reduction in spontaneous speech, and more prominent deficits of praxis and episodic memory, but fewer speech errors and less marked impairment of literacy skills. This pattern of clinical and cognitive deficits in PSP-PNFA is consistent with the relatively greater involvement of prefrontal areas and less marked involvement of perisylvian areas visualised in the cortical thickness analysis of the PSP-PNFA cases. However, it is noteworthy that more severe midbrain atrophy was observed in the PSP-PNFA group than the PNFA-only group: midbrain atrophy here is likely to represent a marker for more extensive involvement of basal ganglia and other subcortical structures in PSP-PNFA. Lesions of subcortical nuclei can themselves give rise to a range of neuropsychological deficits (39). Furthermore, pathological examination in cases of PSP with progressive aphasia/apraxia of speech has demonstrated grey matter atrophy predominantly affecting the superior premotor cortex spreading to the bank of the precentral gyrus and supplemental motor area and other frontal regions, as well as the caudate nuclei and the globus pallidus (7). Considering these lines of evidence together, it is therefore plausible that a conjunction of cortical and subcortical damage determines the neuropsychological profile in PSP-PNFA.

Though subject to ascertainment bias, the present study suggests a prevalence of PSP-PNFA of the order of 29% of all cases of PNFA. Although our cases have not been pathologically confirmed, they share a number of clinical and neuroradiological similarities with pathologically proven cases in the PSP spectrum. A review of the presenting clinical features of the 170 cases of pathologically-confirmed PSP in the Queen Square Brain Bank database revealed four cases with speech or language problems at presentation although no detailed clinical assessments were available on these patients. These retrospective data suggest an approximate prevalence of PSP-PNFA of at least 2% of all pathologically-confirmed PSP: this is likely to be an underestimate, due to incomplete data recording and ascertainment bias (the majority of cases were recruited and assessed via a specialist movement disorders clinic). Previous work has demonstrated that diseases in the FTL spectrum may show evolution of the clinical phenotype over the course of the illness: patients may present with a particular syndrome, and subsequently develop features of another syndrome. In one series of 60 patients with FTL (40), 22 initially presented with

PPA: of these 9 developed features suggestive of PSP/CBS during the course of the disease, however none had specific PSP pathology at post mortem. One case presenting as typical PSP clinically developed progressive aphasia as a late manifestation and was found to have histopathological features of PSP. Taken together with the evidence of previous cases of speech-led presentations of pathologically proven PSP (Table 3), it is possible that progressive aphasia is more commonly underpinned by PSP pathology than is widely recognised. On the other hand, a proportion of these cases have ‘atypical’ features histopathologically, and the role of such anomalies in modifying the clinical phenotype has not been defined. There are several potential sources of bias in work of this kind. Patients presenting with progressive aphasia may not undergo comprehensive general neurological examination later in the illness, patients with PNFA in whom clinical features of PSP rapidly supervene may be less frequently included in pathological series of FTL cases, while patients with classical PSP who develop speech or language deficits later in the illness may not have detailed neuropsychological assessment. Conversely, it is unclear what proportion of ‘typical’ PNFA cases may have ‘subclinical’ features of the PSP syndrome: this would entail a detailed (longitudinal) analysis of oculomotor function in all patients presenting with PNFA, which we did not undertake here. These observations further underline the need for detailed longitudinal studies with pathological correlation in patients presenting with PNFA and PSP. It would also be of interest to assess the behavioural and neuropsychiatric features of these cases in more detail: the relatively greater prefrontal and subcortical involvement in PSP-PNFA would predict a greater prominence of abulia or adynamia in these patients compared with other PNFA cases.

Taking these caveats into account, the present study suggests the existence of a fourth clinico-anatomical variant of PSP, in line with previous calls for greater recognition of this syndrome (4,7). The PSP-PNFA syndrome is of both clinical and neurobiological importance. Clinically, the patient with progressive speech apraxia and early marked impoverishment of propositional speech without prominent speech errors should be observed closely for development of the PSP syndrome. Neurobiologically, such cases suggest that PSP should no longer be regarded as a paradigmatic ‘subcortical’ dementia: rather (analogously with other neurodegenerative disorders, such as dementia with Lewy bodies and corticobasal degeneration) it represents a spectrum of overlapping syndromes that may have a cortical emphasis at presentation.

Acknowledgments

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health’s NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer’s Research Trust Co-ordinating Centre. This work was also funded by the Medical Research Council UK. JDR is supported by a Brain Exit Scholarship. SSO is supported by the Reta Lila Weston Trust. JDW is supported by a Wellcome Trust Intermediate Clinical Fellowship.

Full Financial Disclosures of all Authors for the Past Year

Full Financial Disclosures of all Authors for the Past Year

Rohrer

Stock Ownership in medically-related fields	none
Consultancies	none
Advisory Boards	none
Partnerships	none
Honoraria	none
Grants	Brain Exit Scholarship
Intellectual Property Rights	none
Expert Testimony	none
Employment	University College London
Contracts	none
Royalties	none
Other	none

Paviour

Stock Ownership in medically-related fields	none
Consultancies	none
Advisory Boards	none
Partnerships	none
Honoraria	none
Grants	none
Intellectual Property Rights	none
Expert Testimony	none
Employment	none
Contracts	none
Royalties	none
Other	none

Bronstein

Stock Ownership in medically-related fields	none
Consultancies	none
Advisory Boards	none
Partnerships	none
Honoraria	none
Grants	MRC
Intellectual Property Rights	none
Expert Testimony	none
Employment	Imperial College London
Contracts	none
Royalties	Cambridge University Press, Arnold Publishers
Other	none

O'Sullivan

Stock Ownership in medically-related fields	none
Consultancies	none

Advisory Boards	none
Partnerships	none
Honoraria	Britannia pharmaceuticals
Grants	Reta Lila Weston Trust
Intellectual Property Rights	none
Expert Testimony	none
Employment	University College London
Contracts	none
Royalties	none
Other	none
Lees	
Stock Ownership in medically-related fields	none
Consultancies	Genus
Advisory Boards	Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion
Partnerships	none
Honoraria	Novartis, Teva, Meda, Boehringer Ingelheim, GSK, Ipsen, Lundbeck, Allergan, Orion
Grants	PSP Association, Weston Trust – The Reta Lila Howard Foundation
Intellectual Property Rights	none
Expert Testimony	none
Employment	UCL/UCLH
Contracts	none
Royalties	none
Other	none
Warren	
Stock Ownership in medically-related fields	none
Consultancies	none
Advisory Boards	none
Partnerships	none
Honoraria	none
Grants	Wellcome Trust Intermediate Clinical
Fellowship	
Intellectual Property Rights	none
Expert Testimony	none
Employment	University College London
Contracts	none
Royalties	none
Other	none

End of financial disclosures

REFERENCES

1. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. Dec; 1998 51(6):1546–54. [PubMed: 9855500]
2. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. Mar; 2004 55(3):335–46. [PubMed: 14991811]
3. Graham NL, Bak T, Patterson K, Hodges JR. Language function and dysfunction in corticobasal degeneration. *Neurology*. Aug 26; 2003 61(4):493–9. [PubMed: 12939423]
4. Josephs KA, Duffy JR. Apraxia of speech and nonfluent aphasia: a new clinical marker for corticobasal degeneration and progressive supranuclear palsy. *Curr Opin Neurol*. Dec; 2008 21(6): 688–92. [PubMed: 18989114]
5. Boeve B, Dickson D, Duffy J, Bartleson J, Trenerry M, Petersen R. Progressive Nonfluent Aphasia and Subsequent Aphasic Dementia Associated with Atypical Progressive Supranuclear Palsy Pathology. *European Neurology*. 2003; 49:72–78. [PubMed: 12584413]
6. Josephs KA, Boeve BF, Duffy JR, et al. Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. *Neurocase*. 2005; 11:283–296. [PubMed: 16093229]
7. Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. *Brain*. Jun 1.2006 129:1385–1398. [PubMed: 16613895]
8. Karnik NS, D'Apuzzo M, Greicius M. Non-Fluent Progressive Aphasia, Depression, and OCD in a Woman With Progressive Supranuclear Palsy: Neuroanatomical and Neuropathological Correlations. *Neurocase*. 2006; 12:332–338. [PubMed: 17182396]
9. Mochizuki A, Ueda Y, Komatsuzaki Y, Tsuchiya K, Arai T, Shoji S. Progressive supranuclear palsy presenting with primary progressive aphasia--Clinicopathological report of an autopsy case. *Acta Neuropathologica*. Jun 1.2003 105:610–614. [PubMed: 12669238]
10. Wakabayashi K, Shibasaki Y, Hasegawa M, et al. Primary progressive aphasia with focal glial tauopathy. *Neuropathol Appl Neurobiol*. Oct.2000 26:477–481. [PubMed: 11054189]
11. Rohrer JD, Knight WD, Warren JE, Fox NC, Rossor MN, Warren JD. Word-finding difficulty: a clinical analysis of the progressive aphasias. *Brain*. Jan.2008 131:8–38. [PubMed: 17947337]
12. Folstein M, Folstein S, McHugh P. The “Mini Mental State”: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
13. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology*. Dec 12; 2000 55(11):1621–6. [PubMed: 11113214]
14. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. Jul; 1996 47(1):1–9. [PubMed: 8710059]
15. Litvan I, Bhatia KP, Burn DJ, et al. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord*. May.2003 18:467–486. [PubMed: 12722160]
16. Payan CVM, Lacomblez L, Viallet F, et al. Neuroprotection and natural history in Parkinson plus syndromes (NNIPPS): construction and validation of a functional scale for disease progression assessment in Parkinson plus syndromes, progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). *Mov Disord*. 2002; 17(suppl 5):256.
17. Blain CR, Barker GJ, Jarosz JM, et al. Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI. *Neurology*. Dec 26; 2006 67(12):2199–205. [PubMed: 17190944]
18. Raven, J.; Raven, JC.; Court, JH. Manual for Raven's Progressive Matrices and Vocabulary Scales. Section 1: General Overview. Harcourt Assessment; San Antonio, TX: 2003.
19. Warrington, EK. The Camden Memory Tests. Psychology Press; 1996.
20. Warrington, EK.; James, M. The visual object and space perception battery. Thames Valley Test Company; Bury St Edmunds, UK: 1991.

21. Reitan, RM. A manual for the administrating and scoring of the Trail Making Test. Indiana University Press; Indianapolis, IN, USA: 1959.
22. Goodglass, H.; Kaplan, E. The assessment of aphasia and related disorders. Lea and Fediger; Philadelphia: 1983.
23. McKenna P, Warrington EK. Testing for nominal dysphasia. *J Neurol Neurosurg Psychiatry*. 1980; 43(9):781–8. [PubMed: 7420102]
24. Warrington EK, McKenna P, Orpwood L. Single word comprehension: a concrete and abstract word synonym test. *Neuropsychol Rehabil*. 1998; 8:143–54.
25. Kay, J.; Lesser, R.; Coltheart, M. Psycholinguistic Assessments of Language Processing in Aphasia (PALPA). Erlbaum; Hove: 1992.
26. McCarthy R, Warrington EK. A two-route model of speech production. Evidence from aphasia. *Brain*. Jun; 1984 107(Pt 2):463–85. [PubMed: 6722512]
27. Snowling, MJ.; Stothard, SE.; McLean, J. Graded nonword reading test. Thames Valley Test; Bury St. Edmunds, UK: 1996.
28. Baxter DM, Warrington EK. Measuring dysgraphia: a graded-difficulty spelling test. *Behav Neurol*. 1994; 7(3–4):107–16. [PubMed: 24487323]
29. Freeborough PA, Fox NC, Kitney RI. Interactive algorithms for the segmentation and quantitation of 3-D MRI brain scans. *Comput Methods Programs Biomed*. 1997; 53(1):15–25. [PubMed: 9113464]
30. Mazziotta JC, Toga AW, Evans A, et al. A Probabilistic Atlas of the Human Brain – Theory and Rationale for Its Development. *Neuroimage*. 1995; 2:89–101. [PubMed: 9343592]
31. Paviour DC, Price SL, Jahanshahi M, Lees AJ, Fox NC. Regional brain volumes distinguish PSP, MSA-P, and PD: MRI-based clinico-radiological correlations. *Mov Disord*. Jul.2006 21:989–996. [PubMed: 16602104]
32. Dale AM, Fischl B, Sereno MI. Cortical Surface-Based Analysis I: Segmentation and Surface Reconstruction. *NeuroImage*. 1999; 9(2):179–194. [PubMed: 9931268]
33. Fischl B, Dale AM. Measuring the Thickness of the Human Cerebral Cortex from Magnetic Resonance Images. *Proceedings of the National Academy of Sciences*. 2000; 97:11044–11049.
34. Rohrer JD, Warren JD, Modat M, Ridgway GR, Douiri A, Rossor MN, Ourselin S, Fox NC. Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration. *Neurology*. May 5; 2009 72(18):1562–9. [PubMed: 19414722]
35. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Annals of Neurology*. 2003; 54:S15–S19. [PubMed: 12833363]
36. Perkin GD, Lees AJ, Stern GM, Kocen RS. Problems in the diagnosis of progressive supranuclear palsy. (Steele—Richardson—Olszewski syndrome). *Can J Neurol Sci*. May; 1978 5(2):168–73. [PubMed: 667744]
37. Williams DR, de Silva R, Paviour DC, et al. Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson’s syndrome and PSP-parkinsonism. *Brain*. Jun.2005 128:1247–1258. [PubMed: 15788542]
38. Williams DR, Holton JL, Strand K, Revesz T, Lees AJ. Pure akinesia with gait freezing: a third clinical phenotype of progressive supranuclear palsy. *Mov Disord*. Nov 15.2007 22:2235–2241. [PubMed: 17712855]
39. Warren JD, Smith HB, Denson LA, Waddy HM. Expressive language disorder after infarction of left lentiform nucleus. *J Clin Neurosci*. Sep; 2000 7(5):456–8. [PubMed: 10942673]
40. Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. *Brain*. Sep 1.2005 128:1996–2005. [PubMed: 16033782]

Figure 1. Cortical thickness maps showing patterns of cortical thinning in disease groups (yellow/red) compared to controls (blue): A) PNFA without PSP and B) PSP-PNFA. No significant areas of thinning were seen in a comparison of PSP-RS and controls. Left hemisphere is shown above, right hemisphere below; for each hemisphere, the top panels are lateral views, the bottom panels medial views. Coloured bar represents FDR corrected p-values

Figure 2. Cortical thickness maps showing patterns of cortical thinning in disease comparisons:
A) PNFA without PSP (yellow/red) versus PSP-PNFA (blue) and B) PSP-PNFA (blue) versus PSP-RS. Left hemisphere is shown above, right hemisphere below with lateral views shown. Left sided pictures represent significance maps with coloured bar representing uncorrected p-values; right-sided maps represent percentage thinning maps with coloured bar representing a percentage value

Table 1
Demographic, general neuropsychological data and neurolinguistic data in patients and healthy controls

	PSP-PNFA *	PNFA without PSP	Controls
Number of subjects	4	10	14
Male:Female	3:1	7:3	8:6
Age (years)	71.2 (5.8)	72.0 (7.4)	69.7 (4.7)
Age at onset (years)	66.0 (6.8)	66.4 (7.9)	N/A
Duration from onset of language symptoms (years)	5.2 (2.5)	5.6 (2.1)	N/A
MMSE score (/30)	26.5 (2.4)	23.0 (6.2) ^a	29.6 (0.9)
FAB score (/18)	8.3 (3.9) ^a	11.0 (4.2) ^a	17.8 (0.4)
<i>Neuropsychological assessment</i>			
Ravens Advanced Matrices IQ	96.3 (23.2) ^a	94.5 (18.5) ^a	113.6 (9.9)
Camden Pictorial Recognition Memory Test (/30)	27.5 (3.0) ^{a,b}	29.5 (0.8)	29.6 (0.9)
Trail making test A (scaled score)	2.5 (1.6) ^a	4.0 (2.2) ^a	9.7 (2.8)
Trail making test B (scaled score)	4.2 (2.1) ^a	3.7 (3.2) ^a	9.8 (2.8)
Visuoperceptual skills – VOSP Object Decision (/20)	16.5 (4.5)	16.4 (2.3)	17.1 (2.4)
Limb apraxia (number of cases)	3	4	0
Digit span forwards	5.0 (1.2) ^a	4.7 (1.3) ^a	7.0 (0.6)
<i>Neurolinguistic assessment</i>			
Words/minute [#]	21.0(12.6) ^a	40.3 (18.1) ^a	133.9 (22.9)
Speech production errors/min [#]	0.2 (0.3)	1.5 (1.7) ^a	0.0 (0.0)
Agrammatic errors/min [#]	0.8 (0.1) ^a	0.6 (0.5) ^a	0.0 (0.0)
Apraxia of speech severity (/3) [#]	1.8 (1.0) ^a	1.8 (0.9) ^a	0.0 (0.0)
Naming (/20)	13.5 (9.1) ^a	11.3 (6.4) ^a	19.7 (0.7)
Single word comprehension - Warrington synonyms test (/50)	40.0 (1.4) ^a	38.1 (6.9) ^a	48.6 (1.3)
Sentence comprehension – shortened PALPA 55 test (/24)	20.0 (13.5) ^a	19.2 (4.3) ^a	23.4 (0.9)
Single word repetition (/30)	22.5 (15.0)	22.0 (10.8) ^a	29.8 (0.4)
Sentence repetition (/10)	6.8 (4.6)	5.3 (4.6) ^a	10.0 (0.0)
Reading – irregular word reading test (/30)	20.0 (13.5)	15.2 (8.1) ^a	28.0 (1.8)
Reading – Graded difficulty nonword reading test (/20)	11.3 (8.4) ^a	8.1 (5.7) ^a	19.6 (0.7)
Spelling – Graded difficulty spelling test (/30)	24.7 (3.2)	7.6 (7.8) ^{a,c}	25.6 (2.8)

N/A – not applicable

^a p<0.05 disease group worse than controls,

^b $p < 0.05$ PSP-PNFA worse than PNFA without PSP,

^c $p < 0.05$ PNFA without PSP worse than PSP-PNFA

[#] Assessed using a spontaneous speech analysis of a description of the patient's last holiday and the Cookie Theft Scene from the Boston Diagnostic Aphasia Examination

^{*} One PSP-PNFA case was mute at the time of assessment

Table 2
Brain volumetric data in patients, controls and a pathologically-confirmed group of patients with classical PSP

	PSP-PNFA (n=4)	PNFA without PSP (n=10)	PSP-RS (n=5)	Controls (n=14)
Brain volume (% of TIV)	65.2 (5.9)	62.1 (4.9) ^a	65.4 (4.1)	69.4 (4.2)
Midbrain volume (% of TIV)	4.2 (0.5) ^{a,b}	5.2 (1.0)	3.1 (0.5) ^{a,c,d}	5.3 (0.6)

^a p<0.05 disease group smaller than controls,

^b p<0.05 PSP-PNFA smaller than PNFA without PSP,

^c p<0.05 PSP (RS) smaller than PSP-PNFA v,

^d p<0.05 PSP (RS) smaller than PNFA without PSP

Table 3
Review of cases from the literature of PSP with progressive aphasia/apraxia of speech in comparison to the four cases presented in this series

Author Nomenclature	N	Sex	Age at onset (years)	Symptoms/Signs at onset	Gaze palsy (duration from onset - years)	Falls (duration from onset - years)	Duration to death (years)	Other symptoms and signs during disease course	Pathological diagnosis
Cases in this series <i>PNFA</i>	4	F	67	Articulatory difficulty: hesitant, effortful speech, confusion between yes and no	+ (3)	+ (3)	N/A	Mild limb bradykinesia and rigidity, limb apraxia	N/A
		M	73	Speech production impairment with word-finding difficulty and hesitancy	+ (3)	+ (1)	N/A	Apathy, depression	N/A
		M	65	Articulatory difficulty with effortfulness and word-finding difficulty. Loss of ability to hum or whistle.	+ (8.5)	+ (8)	N/A	Mild parkinsonian syndrome, with right limb myoclonus and limb apraxia	N/A
		M	57	Decreased speech amount with hesitancy and effortfulness in speech production	+ (5)	+ (4)	N/A	Limb apraxia	N/A
Karnik et al. 2006 <i>PNFA</i>	1	F	62	Apathy, anhedonia, worsening depression, effortful non-fluent speech	-	+ (2)	4	Severe OCD since aged 40yrs, falls in context of post surgical foot drop.	PSP
Josephs et al. 2006 <i>Progressive aphasia/AOS*</i>	2	F	69	AOS.	+ (onset not recorded)	-	9	Limb apraxia, rigidity and bradykinesia.	Atypical PSP
		M	74	AOS.	-	-	8	Limb apraxia, rigidity and bradykinesia.	Atypical PSP
		F	77	Naming difficulty and non-fluent speech.	+ (2)	+ (3)	5	Mild asymmetric spasticity, axial rigidity.	Atypical PSP Hippocampal sclerosis Braak stage I
Josephs et al. 2005 <i>AOS PNFA</i>	4	F	53	Articulatory difficulty, AOS, emotional lability.	-	-	8	Late obsessional behaviour, brisk reflexes.	Atypical PSP Braak stage III
		F	69	Difficulty with pronunciation, confusion between yes/no.	+ (4)	-	8	Head tremor, brisk reflexes. Family history of motor neuron disease and dementia.	Atypical PSP Braak stage IV-V Transitional LB
		M	70	Anomia, hesitancy, paragrammatic errors, AOS.	-	-	7	Mild hypomimia, late behavioural problems.	Atypical PSP Amyloid angiopathy
Boeve et al. 2003 <i>PNFA</i>	1	M	71	Anomia, AOS.	-	+ (5-6)	6	Mild Parkinsonism, agitation.	Atypical PSP Amyloid angiopathy

Author Nomenclature	N	Sex	Age at onset (years)	Symptoms/Signs at onset	Gaze palsy (duration from onset - years)	Falls (duration from onset - years)	Duration to death (years)	Other symptoms and signs during disease course	Pathological diagnosis
Mochizuki <i>et al.</i> 2003 PPA	1	M	64	Difficulty with spontaneous speech on the telephone.	-	+ (10)	10	Right upper limb clumsiness, brisk reflexes. Repetitive behaviour.	PSP
Wakabayashi <i>et al.</i> 2000 PPA	1	M	72	"Aphemia", decreased speech output	-	NR	6	No other early signs. Late right hemisphere (temporal/occipital) stroke.	PSP
Perkin <i>et al.</i> 1978 PSP with dysphasia	2	F	57	Speech production difficulties	NR	NR	N/A	Right upper limb tremor and rigidity	N/A
		F	58	Non-fluent dysphasia	NR	NR	N/A	Right upper limb rigidity	N/A

PSP – progressive supranuclear palsy, PPA – primary progressive aphasia, PNFA – progressive non-fluent aphasia, AOS – apraxia of speech, NR – not recorded, N/A – not applicable, OCD – obsessive compulsive disorder.

* cases not already described in previous publication by the same authors (Josephs *et al.*, 2005).

Table 4
Comparison of age of onset, disease duration and age at death in the different PSP phenotypes: present PSP-PNFA cases are compared with previous PSP cohorts in references [37, 38]

	Clinical presentation	Age at onset	Disease duration	Age at death
PSP-PNFA	Difficulty with speech production	64.9 (7.2)	6.7 (2.0)	73.8 (7.0)
PSP-RS	Gaze palsy, axial rigidity and falls	66.5 (7.4)	6.3 (2.4)	72.8 (7.1)
PSP-P	Asymmetric tremor, late falls and gaze palsy	63.2 (9.9)	11.7 (4.9)	74.9 (9.3)
PAGF	Gradual onset of freezing of gait	61 (age range 44-78)	13 (age range 5-21)	NR

NR – not recorded